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Treatment of patients with cocaine-induced arrhythmias: bringing the bench to the bedside

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Widespread use of cocaine and its attendant toxicity has produced a wealth of benchwork studies and small animal investigations that evaluated the effects of cocaine on the cardiovascular system. Despite this wealth of knowledge, very little is known about the frequency or types of arrhythmias in patients with significant cocaine toxicity. The likely aetiologies; catecholamine excess, sodium channel blockade, potassium channel blockade, calcium channel effects, or ischaemia may act alone or in concert to produce a vast array of clinical findings that are modulated by hyperthermia, acidosis, hypoxia and electrolyte abnormalities. The initial paper in the series by Wood & Dargan providing the epidemiological framework of cocaine use and abuse is followed by a detailed review of the electrophysiological effects of cocaine by O'Leary & Hancox. This review is designed to complement the previous papers and focuses on the diagnosis and treatment of patients with cocaine-associated arrhythmias.

Introduction

Despite robust animal and basic science research, little epidemiological or clinical data are available with regard to the incidence or types of arrhythmias in cocaine users [1]. This research is clearly hampered by deaths in cocaine users who never reach health care, some of which almost certainly represents sudden death from malignant arrhythmias that occur during maximal cocaine concentrations [2]. In dogs, virtually every type of rhythm disturbance known can be produced by cocaine, some in a dose-dependent fashion [3]. Similarly in human case reports cocaine use is associated with a variety of arrhythmias that include the full spectrum of possibilities from benign sinus tachycardia to the most consequential arrhythmias including ventricular tachycardia, torsade de pointes and ventricular fibrillation.

O'Leary & Hancox [4] eloquently demonstrate that in experimental models, cocaine and some metabolites interact with cardiac sodium, calcium and potassium channels. The blockade of cardiac sodium channels is somewhat predictable given the local anaesthetic effects of cocaine (resulting from neuronal sodium channel blockade) and the homology between cardiac and neuronal sodium channels. In contrast, potassium channel blockade cannot be anticipated from the other known pharmacological effects of cocaine and most likely results from the promiscuous nature of cardiac potassium channels. While many drugs that block cardiac sodium channels also block cardiac potassium channels, most neuronal sodium channel blockers (local anaesthetics) have little or no clinically relevant effects on cardiac potassium channels.

In intact organisms two other mechanisms may be important in the genesis of cocaine-induced arrhythmias. First, cocaine increases concentrations of circulating catecholamines [5] which typically increase heart rate. Since sodium channel blockade follows use-dependent kinetics, increases in heart rate exacerbate sodium channel blockade. Additionally, tachycardia alone may be sufficient to trigger a re-entrant rhythm in a susceptible host. Secondly, cocaine can cause ischaemia and infarction [6, 7]. Ischaemia and infarction result in dispersion of repolarization, which creates a substrate for arrhythmia. Thus in the model that requires both substrate and trigger to produce an arrhythmia [8], cocaine is somewhat unique in its ability to provide both necessary elements. Blockade of either sodium channels, potassium channels or both, with or without attendant ischaemia is sufficient to produce a susceptible substrate, and tachycardia from catecholamine excess or psychiatric agitation serves as an ever present trigger. The resultant arrhythmia is related to a variety of host factors that not only includes dose, co-exposures to other drugs, acid-base and electrolyte balance and possibly genetic variability in either cocaine metabolism, and

either ion channel structure or function. This discussion will begin with a focus on arrhythmias that result from the acute inhibitory effects of cocaine on cardiac ion channels. A step-wise approach to treatment will be presented based on existing evidence. Finally, non-ion channel effects and their treatments will be discussed.

Sodium channel blockade

The blockade of fast inward sodium channels by cocaine is best described as a class IC effect according the Vaughn-Williams classification of anti-arrhythmic agents. Stated another way, binding is relatively slow both in onset and offset [9]. The upstroke of the action potential is delayed with resultant prolongation of conduction and impaired myocardial contractility. Heart rate and acid-base status are significant modulators of the effects of cocaine – increases in heart rate and decreases in pH both increase the degree of sodium channel blockade [10, 11].

Manifestations on the surface electrocardiogram can range from very subtle findings to quite overt abnormalities and resemble events described with other sodium channel blocking toxins, most notably the tricyclic antidepressants. Conduction on the right side is preferentially impaired. Although several theories have been advanced to explain this finding (mostly related to either variations in the channel density, distribution or structure) none is sufficiently supported by definitive evidence to warrant further discussion. Findings consistent with early or minimal toxicity involve a rightward axis shift of the terminal 40 ms of the QRS complex. This is most easily detected as an 'S' wave in leads I and aVL and an 'R' wave in lead aVR (Figure 1) and can be accompanied by in incomplete right bundle branch block pattern in the precordial leads. This pattern, originally described in patients with tricyclic antidepressant overdose [12] is now recognized as a non specific manifestation of sodium channel blockade. As toxicity increases, an overt right bundle branch pattern may develop, which is occasionally confused for ventricular tachycardia. Although true ventricular tachycardia can result from cocaine use, it seems comparatively uncommon. The more common wide-complex tachycardia that results from sodium channel blockade (Figure 2) can often be distinguished from ventricular tachycardia either by standard criteria such as Wellens or Brugada [13], or more commonly by its frequently changing heart rate and QRS morphology and response to bicarbonate therapy (see below) all of which are inconsistent with a re-entrant ventricular tachycardia. It is important to note that no study has systematically evaluated the electrocardiographic findings in a large group of patients with acute cocaine toxicity. A small study suggests that tachycardia is the most common finding, and that asymptomatic patients often have QRS prolongation, which may result from underlying heart disease [14]. In a few patients who have used cocaine

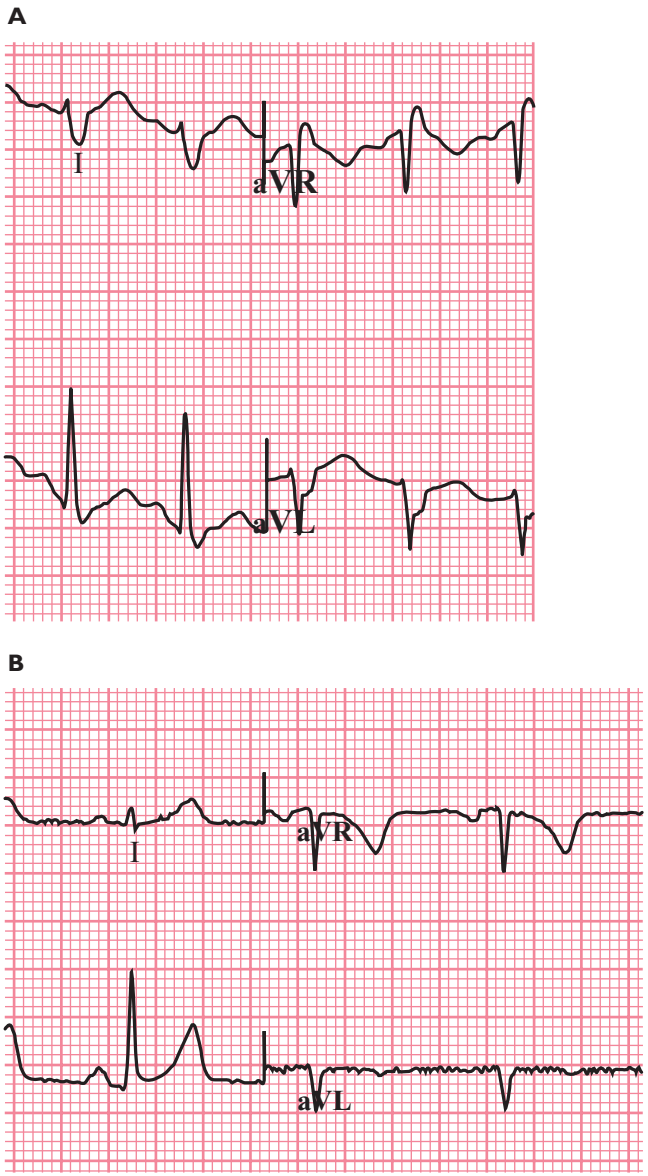

Figure 1

Figure 1A demonstrates the early sodium channel blocking effects of cocaine. Specifically demonstrated are the presence of an S wave in leads I and aVL and an R wave in lead aVR. The QRS duration is slightly prolonged at approximately 120 ms. Figure 1B shows the the ECG on the same patient from Figure 1A immediately following the infusion of 44 mEq of hypertonic sodium bicarbonate. Note that the QRS duration has narrowed significantly and that the changes in leads I, aVL and aVR have essentially normalized

a classic Brugada pattern has been noted [15–17]. Although unstudied, it is quite likely that these patients express a sodium channel mutation described in association with Brugada abnormality and that the sodium channel blocking properties of cocaine made the patients' underlying physiological abnormality more evident.

As noted previously, heart rate is one major modulator of the degree of sodium channel blockade produced by

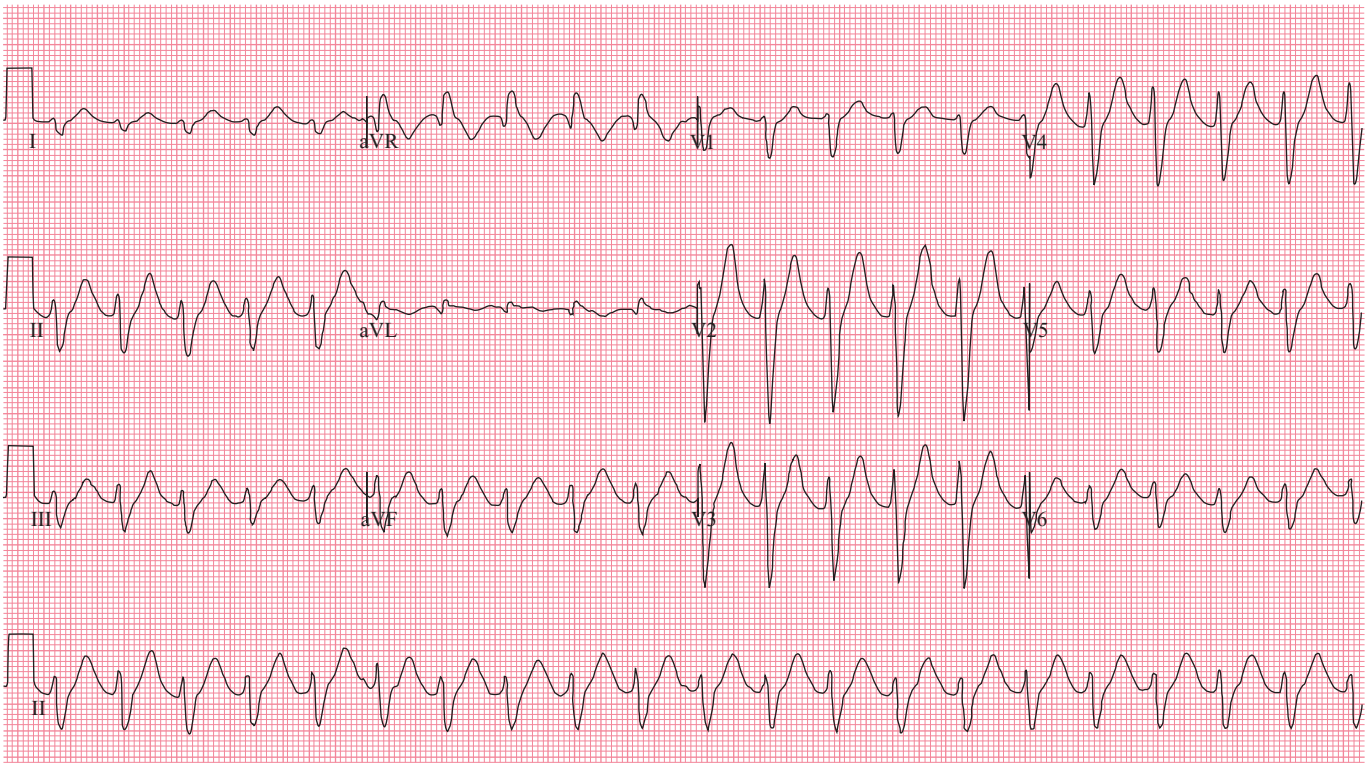

Figure 2

Figure 2 shows a wide-complex tachycardia most likely resulting from sodium channel blockade in a patient with clinical signs and symptoms of acute cocaine toxicity. Note again the prominent R wave in lead aVR. This patient was treated simultaneously with oxygen, diazepam, hypertonic sodium bicarbonate and intravenous fluids, and the ECG normalized

cocaine. However, it is important to note that tachycardia is not necessarily associated with sodium channel blockade. Although some degree of negative inotropy follows the impaired influx of sodium and a compensatory tachycardia would be expected, this is usually mild. In fact, much of the tachycardia associated with toxicologic sodium channel blockade appears to result from the complex pharmacology of sodium channel blocking drugs. For example, tricyclic antidepressants are also potent α-adrenergic antagonists and antimuscarinic agents, producing vasodilation and tachycardia. With regards to cocaine, tachycardia likely results from central nervous system agitation and increased catecholamines. Several examples best illustrate this point. First, in anaesthetized animals the heart rate remains largely unchanged and the arrhythmic effects of small (sub-lethal) doses of cocaine are minimized [18]. In contrast massive doses of cocaine in humans occasionally result from rupture of smuggled drug packets. At these high doses, blockade of neuronal conduction impairs central nervous system response. Heart rate remains normal or bradycardia results. The surface electrocardiogram may show junctional rhythm with a somewhat widened QRS complex and prominent T-waves [17]. Similar effects occur in research animals (Figure 3) Many clinicians have noted that these changes resemble hyperkalaemia, which also produces sodium channel blockade.

Treatment of arrhythmias resulting from cocaine-associated sodium channel blockade

Treatment of patients with wide-complex tachycardia related to cocaine is based on sound animal experiments but only supported by limited human data. Dogs given cocaine develop prolongation of their QRS complex which is reversed by hypertonic sodium bicarbonate [19]. In a similar series of experiments animals were poisoned with cocaine until significant widening of the QRS complex developed [20]. At that point either hypertonic sodium bicarbonate, lidocaine or quinidine were administered. While quinidine (a class IA anti-arrhythmic agent) resulted in further prolongation of the QRS duration, both hypertonic sodium bicarbonate and lidocaine improved conduction. The effects of lidocaine and quinidine are consistent with their known anti-arrhythmic properties. Since the class IA and IC drugs both express slow offset and use dependent blockade, their effects could be expected to be additive or even synergistic. In contrast, lidocaine (a class IB anti-arrhythmic agent) has a rapid offset and is rarely associated with QRS prolongation in either therapeutic or

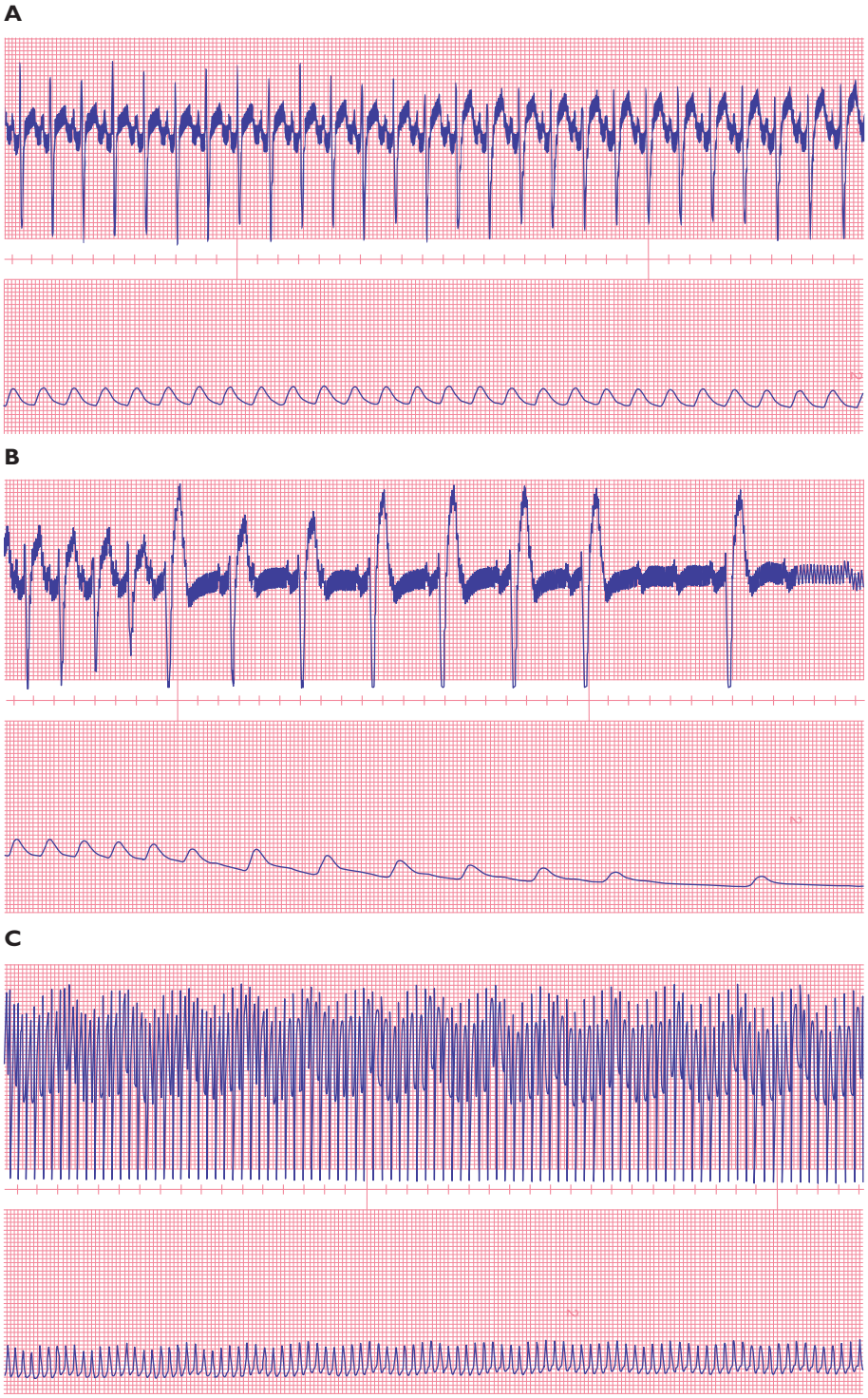

Figure 3

Rabbits were intubated endotracheally and sedated with xylazine. Figure 3A demonstrates the heart rate (and corresponding blood pressure following an LD_{10} dose of cocaine. The heart rate increases from baseline (120 beats min^{-1}) to nearly 200 beats min^{-1}. In Figure 3B a larger (LD_{90}) dose of cocaine is given. The heart rate slows, the QRS prolongs, the T waves become large and peaked (as in hyperkalaemia), the blood pressure falls and heart block develops. In Figure 3C, the rabbit from Figure 3B has been given 100% oxygen and 1 mEq kg^{-1} of hypertonic sodium bicarbonate. A regular rhythm returns at a rate of nearly 300 beats min^{-1} (note the speed of the chart recorder was changed to capture more information) with a narrow QRS complex and restoration of blood pressure

overdose situations [9]. In fact, lidocaine has been used successfully to treat wide complex dysrhythmias in patients with toxicity from other sodium channel blockers such as propoxyphene [21] and tricyclic antidepressants [22, 23]. Since lidocaine can compete with cocaine for binding to the sodium channel, and if successful will rapidly dissociate allowing for recovery, improved conduction will result.

While clinical improvement with hypertonic bicarbonate has been reported in humans [11, 24, 25], these reports are often potentially confounded by the presence acidosis and the semi-simultaneous administration of multiple therapies. Lidocaine use in humans with cocaine toxicity is often considered controversial because of the potential for additive proconvulsant effects of lidocaine and cocaine. Animal data on this point are contradictory with a canine model demonstrating increased seizures and death [26] and a murine model confirming the convulsant effects of lidocaine in cocaine treated animals, but demonstrating improved survival [27]. Additionally, in some models lidocaine is only effective in doses that would be clearly toxic to humans [28]. More convincingly, clinical experience with lidocaine in patients with cocaine-associated acute coronary syndromes has not only been beneficial, but was not associated with seizures [29].

The clinical scenario may help provide a reasonable approach to management. Patients with wide complex tachycardia related to cocaine should be divided into those who appear acutely cocaine toxic or not, based on the presence of hypertension, tachycardia, diaphoresis, mydriasis and psychomotor agitation. When overt cocaine toxicity is present and the QRS is significantly prolonged, it is reasonable to assume that patients are suffering primarily from sodium channel blockade. Oxygenation and ventilation should be optimized and rapid cooling begun when extreme hyperthermia is present. Sedation with a benzodiazepine is indicated both to control behaviour and safely lower heart rate which may be sufficient to improve conduction. Hypertonic sodium bicarbonate administration should follow rapidly if the QRS complex remains substantially prolonged. The optimal dose and duration of therapy has never been established but many authorities would give 1–2 mEq kg^{-1} as a bolus, followed either by intermittent boluses as needed or a continuous infusion of isotonic sodium bicarbonate at an infusion of twice the patient's maintenance fluid rate. This is generally continued for several hours as other parameters are optimized and cocaine metabolism occurs or until the QRS duration remains normal and the patient's clinical status improves. Cautions associated with hypertonic sodium bicarbonate use centre around acid base and electrolyte abnormalities. It should be noted that in the setting of sodium channel blockade, experience demonstrates that QRS duration continually narrows as pH increases. Since there are no data to define an optimal QRS duration, the degree of alkalinization should be governed more by safety than by efficacy. As pH rises haemoglobin unloading of oxygen decreases and ionized calcium falls, both of which can be detrimental. Thus by convention it should be uncommon to raise the pH above 7.50 or 7.55 [30]. If this pH is achieved and significant clinical improvement has not occurred, other options should be considered. However, unlike experience with tricyclic antidepressants, there is no experimental or clinical support for the use of hypertonic sodium chloride [31]. Additionally, excessive bicarbonate administration may lead to hypokalemia which can exacerbate potassium channel blockade (see below) and should therefore be avoided. If bicarbonate fails it is reasonable to administer lidocaine in standard anti-arrhythmic doses; typically as a bolus of 1–1.5 mg kg^{-1} repeated every 3–5 min to a maximum of 300 mg, followed by a continuous infusion of 1–4 mg min^{-1}. All IA and IC anti-arrhythmic agents are contraindicated. Although not definitive, early investigation of the use of amiodarone in cocaine toxic animals has not been encouraging [32].

True ventricular tachycardia can frequently be distinguished from aberrantly conducted sinus tachycardia discussed above and should be suspected based on clinical and electrocardiographic findings. When time permits, standard analyses should be performed on the surface electrocardiogram [13]. Additionally, in the setting of cocaine associated myocardial ischaemia and infarction patients will often lack typical clinical findings of cocaine toxicity and wide complex tachycardia is more likely to represent a re-entrant rhythm (ventricular tachycardia) than the aberrantly conducted tachycardia that results from sodium channel blockade. Patients should be given oxygen and assisted ventilation if necessary. Benzodiazepines should be administered for their effects on agitation and heart rate as above and for their additional anti-anginal effects in patients with cocaine associated acute coronary syndromes [33, 34] as well as their anticonvulsant effects. Lidocaine becomes the preferred drug with hypertonic sodium bicarbonate reserved for lidocaine failures. Once again all IA and IC anti-arrhythmic agents as well as β-adrenergic receptor antagonists are contraindicated [35, 36] and the use of amiodarone is unsupported. Electrical cardioversion should be considered for unstable or refractory patients.

Experience with patients who develop Brugada patterns on their electrocardiograms following cocaine use is limited. Under most circumstances the electrocardiogram reverts towards normal as drug toxicity resolves [16]. It is unclear as to whether any therapy is either necessary or effective. Since the major concern is that these people may be at very high risk for sudden arrhythmic death, our practice is to refer them all to an electrophysiologist for evaluation and consideration of an implantable defibrillator. Additionally here, as in all cases, we emphasize cocaine abstinence and refer patients to detoxification programmes whenever they are willing.

Potassium channel blockade

In contrast to sodium channel blockade which is responsible for impaired depolarization, potassium channel blockade impairs repolarization. On the surface electrocardiogram potassium channel blockade is best recognized as prolongation of the QT interval. Several sources of confusion and controversy deserve discussion here. Since sodium channel blockade prolongs the duration of the QRS complex, and the QRS complex is included in the QT interval, QRS prolongation can prolong the QT interval. This finding is compounded by the fact that many sodium channel blocking drugs (including members of the type IA and IC anti-arrhythmic agents) are also known potassium channel blockers. Drugs that exclusively block cardiac potassium channels increase the QT interval without prolonging the QRS complex. Since cocaine blocks both channels it is important when evaluating the electrocardiogram to attempt to ascertain which effect is predominating. Often, the QRS complex duration is essentially normal. Another clue is that when the QT interval is significantly prolonged as a result of potassium channel blockade the T wave frequently takes on an atypical morphology.

Blockade of the rectifying potassium channels impairs repolarization leaving the cell far from the resting (hyperpolarized) state, which allows calcium ions to accumulate in the intracellular cytosol. If sufficient amounts of the positively charged calcium ions accumulate the membrane may oscillate in the positive direction or depolarize. The resultant early or delayed afterdepolarizations may appear on the surface electrocardiogram as abnormal T-waves or U-waves (early afterdepolarizations) or small extra P-waves (delayed afterdepolarizations). These small fluctuations in membrane potential occur during the relative refractory period – a time when some cells might be able to conduct a new impulse. If an afterdepolarization of significant magnitude occurs at a time when a critical number of cells can conduct an impulse an ectopic beat occurs, which can trigger a re-entrant rhythm. Afterdepolarizations are present in experimental models of cocaine administration and are proposed as one possible mechanism responsible for either monomorphic ventricular tachycardia or torsades des pointes [37].

The QT interval was studied in 45 cocaine users with and without chest pain syndromes [38]. Although only mean values were reported, QT prolongation was common, and three patients with prolonged QT developed torsades de pointes. Similarly, when the electrocardiographic findings of 38 patients with acute cocaine toxicity were studied, 10 (26%) were found to have QT prolongation [14]. Additional case reports clearly document QT prolongation and torsade de pointes in the absence of co-exposure to other drugs, or resulting from ischaemia, or combined cocaine use with drugs known to prolong QT, such as methadone [39–44]. Several possibilities must be considered to explain the rarity of reports of consequential QT prolongation and torsades de pointes. It is possible that insignificant QT prolongation is fairly common and therefore overlooked and that consequential QT prolongation only occurs in individual who are otherwise predisposed. Alternatively, QT prolongation might explain many of the deaths associated with cocaine use in patients who never survive to the hospital and therefore have no electrocardiogram obtained. One additional consideration is that although QT prolongation exists, the tachycardia that is commonly associated with cocaine toxicity may be protective against many arrhythmias because increasing the heart rate decreases the relative refractory period thereby lessening the arrhythmic substrate.

Treatment of arrhythmias resulting from cocaine-associated potassium channel blockade

Some patients will manifest QT prolongation or arrhythmias associated with QT prolongation that will require therapy. Unfortunately data are insufficient to make specific recommendations with regard to cocaine and clinicians must rely on treatments applied to QT prolongation from other causes. Electrolyte abnormalities such as hypokalaemia or hypomagnesaemia should be identified and corrected. Unstable rhythms should be treated electrically with cardioversion or defibrillation according to existing protocols. Successful therapies used in patients with cocaine-induced torsades des pointes include overdrive pacing, magnesium, and lidocaine, but data are insufficient to make firm conclusions about the relative efficacies of these therapies [38, 39, 43]. The threshold for prophylactic magnesium in stable patients with QT prolongation from cocaine remains unstudied, but we typically advise therapy in those patients with a corrected QT interval above 500 ms, or who fall above the QT-heart rate pair nomogram when heart rate is too high to allow correction using standard formulas [45].

Catecholamine excess and psychomotor agitation

Increased circulating catecholamine concentrations likely result from blockade of their re-uptake and increased release from central nervous system stimulation [5, 46, 47]. This typically produces supraventricular rhythms, most commonly sinus tachycardia but also re-entrant supraventricular tachycardia and atrial fibrillation. In the previously mentioned series of emergency department patients with acute cocaine toxicity sinus tachycardia was common, and supraventricular tachycardia was present in 5% [14]. Atrial fibrillation has only been noted in case reports and case series [48, 49]. Additional causes of these rhythms can

include psychomotor agitation, psychiatric distress, hyperthermia and volume depletion. As noted above, in animals virtually any rhythm can occur, and is highly dependent on the animal species, the dose of cocaine, and whether sedation is given [3].

Treatment of arrhythmias resulting from cocaine-associated catecholamine excess

Supportive care is generally sufficient for sinus tachycardia and should include sedation with a benzodiazepine, oxygen, cooling and volume resuscitation as clinically indicated. Although no comparative trials exist, diazepam and midazolam are generally preferable to lorazepam because of their rapid peak sedative effects [50, 51]. Midazolam is particularly attractive because its short duration of effect more closely matches the toxicodynamics of cocaine and is therefore less likely to produce oversedation when cocaine has worn off. It is reasonable to start with 1–2 mg doses of midazolam (or 5–10 mg doses of diazepam) intravenously with repeat dosing every 3–5 min until sedation occurs. When intravenous access has not yet been achieved either midazolam (5–10 mg) or lorazepam (2–4 mg) intramuscularly may be acceptable [52–54]. Diazepam should not be given intramuscularly because of erratic absorption [54–56].

Some clinicians are still tempted to control sinus tachycardia especially when consequential hypertension is present. Although it may seem intuitive that the optimal pharmacological approach to the patient with hypertension and tachycardia in the setting of catecholamine excess would involve the use of a β-adrenoceptor antagonist, sound animal and human research demonstrates the catastrophic risks that serve as the basis for the absolute contraindication attached to the use of β-adrenergic receptor antagonists in the setting of cocaine toxicity [57–61]. To summarize, β-adrenergic receptor antagonists exacerbate coronary vasoconstriction, are unpredictable at controlling blood pressure and contribute to lethality in both animals and humans. The reader is referred to a recent guideline and summary of these issues for further detail [36, 62].

If sedation, oxygen, cooling and volume resuscitation fail to control heart rate another aetiology should be sought. For isolated hypertension requiring therapy (such as in the setting of intracranial haemorrhage, aortic dissection, or myocardial infarction) direct acting vasodilators (such as phentolamine or nitroglycerin) should be used followed by rapidly acting titratable calcium channel blockers (nicardipine) if reflex tachycardia develops. For re-entrant supraventricular tachycardia the use of a calcium channel blocker is often required. A similar approach may be necessary for control of the heart rate in patients with atrial fibrillation or atrial flutter. Short acting agents are preferred as many patients revert to normal sinus rhythm as their toxicity resolves.

Ischaemia and infarction

Cocaine-associated myocardial ischaemia and infarction is a multifactorial process that results from increased demand, vasospasm, impaired vasodilation, enhanced coagulation, impaired thrombolysis and accelerated atherogenesis [63]. Multiple reports and case series describe patients who develop myocardial infarction in close temporal association with cocaine use; only a few are cited for the reader to review [6, 7, 48, 64]. In all of these series and additional individual case reports some patients developed ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Once present, ischaemia or infarction alone may be sufficient to cause ventricular arrhythmias. The catecholaminergic effects of cocaine may serve as additional triggers on the substrate of an already vulnerable myocardium. Additionally, cocaine-induced increase in intracellular calcium could be contributory.

Treatment of arrhythmias resulting from cocaine-associated myocardial ischaemia and infarction

Animal models give guidance to potential therapies for cocaine-associated malignant ventricular rhythms. In dog models of ischaemia followed by cocaine use verapamil, nifedipine and diltiazem all protected against ventricular arrhythmias [65, 66]. In these models magnesium was also effective. In a similar investigation, α-adrenergic blockade was also effective, but β-adrenergic blockade was not [67]. In humans, the benefits of α-adrenergic blockade (phentolamine) have been demonstrated experimentally with regard to reversal of cocaine-induced coronary vasoconstriction [68] and clinically with regard to reversal of acute coronary syndrome [69, 70], but not with regard to arrhythmias. As mentioned previously, data suggest safety and efficacy of lidocaine in humans [29], contraindications exist for β-adrenergic antagonists, and both type IA and IC antiarrhythmic agents. Although data on amiodarone are not supportive, evidence of harm is also lacking [32]. The use of magnesium is interesting, but unsupported by any human data.

Patients with unstable rhythms should have oxygenation and ventilation rapidly maximized, followed by prompt cardioversion or defibrillation as is clinically needed. Stable patients should be treated with lidocaine or magnesium followed by a trial of hypertonic sodium bicarbonate. Treatment for ongoing ischaemia should be maximized as described elsewhere [62].

Summary

Complex mechanisms underlie the generation of arrhythmias in patients with acute cocaine toxicity. A safe approach begins with simple supportive care that always includes sedation, oxygenation, volume resuscitation and

correction of electrolyte abnormalities. A careful evaluation of the electrocardiogram interpreted in the clinical context of the patient will guide subsequent therapy. In all cases the use of β-adrenergic antagonists and both types IA and IC anti-arrhythmic agents are contraindicated as is the use of mixed α- and β-adrenergic antagonists. Although probably not contraindicated, the use of amiodarone cannot be supported based on a very limited amount of evidence. Wide complex tachyarrhythmias generally respond to hypertonic sodium bicarbonate and QT prolongation is typically treated first with magnesium. Lidocaine appears safe for re-entrant ventricular rhythms, especially in patients pretreated with benzodiazepines. As cocaine toxicity is a dynamic process patients are best served by close observation in intensive care or a step-down unit until stability has been assured. When the patient is ready for discharge referral to a detoxification programme is likely the most important intervention to help prevent recurrent events.

Competing interests

None declared.

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